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(21) International Application Number: PCT/GB00/02357

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HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
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CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

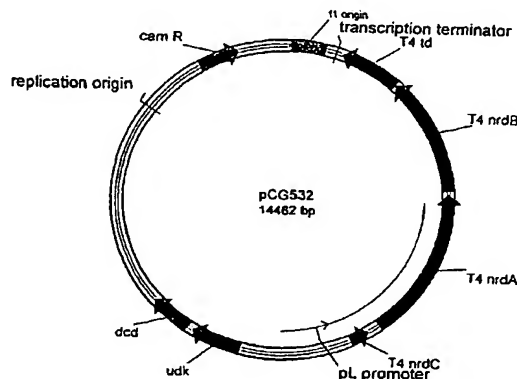
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KOVYROV, Sergey [RU/US]; 11216 Trippon Court,

Published:
— With international search report.

[Continued on next page]

(54) Title: VECTORS, CELLS AND PROCESSES FOR PYRIMIDINE DEOXYRIBONUCLEOSIDES PRODUCTION



(57) Abstract: Novel DNA constructs and host cells comprising the same are disclosed. DNA constructs comprise a transcription unit (e.g. operon) comprising DNA sequences encoding for ribonucleotide reductase and thioredoxin or a uridine kinase gene and/or a dCTP deaminase gene. In preferred embodiments the constructs comprising DNA sequences encoding for ribonucleotide reductase and thioredoxin further comprise DNA sequences encoding for thymidylate synthase and/or transcription units comprising sequences encoding for uridine kinase preferably together with dCTP deaminase. In particularly preferred embodiments, the host cells comprise constructs having all of the above characteristics wherein the host cell displays repressed or no uracil DNA glycosylase activity. This may be achieved by removal of the host cell *ung* gene. Use of host cells in the manufacture of pyrimidine deoxyribonucleotides e.g. thymidine is also disclosed.

WO 01/02580 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PL3813

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) P1049/GW/THY

Box No. I TITLE OF INVENTION

VECTORS, CELLS AND PROCESSES FOR PYRIMIDINE DEOXYRIBONUCLEOSIDES PRODUCTION

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 0NN
GB

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ANDERSON DAVID MARTIN
13601 CHERRYDALE DRIVE
ROCKVILLE
MARYLAND 20859
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

US

State (that is, country) of residence:

US

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

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☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

STRATAGEM INTELLECTUAL PROPERTY MANAGEMENT
THE OLD RECTORY
NEDGING TYE
IPSWICH
IP7 7HQ
GB

Telephone No.

44(0)1449743155

Facsimile No.

44(0)1449743156

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

LIU LIN
18716 CALYPSO PLACE
GAITHERSBURG
MARYLAND 20879
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
CN

State (that is, country) of residence:
US

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

PODKOVYROV SERGEY
11216 TRIPPON COURT
GAITHERSBURG
MARYLAND 20878
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
RU

State (that is, country) of residence:
US

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

WANG BAOMIN
18716 CALYPSO PLACE
GAITHERSBURG
MARYLAND 20879
US

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
CN

State (that is, country) of residence:
US

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

☐ applicant only

☐ applicant and inventor

☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

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☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

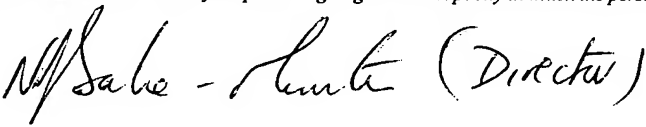
Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | |
|---|--|
| <input checked="" type="checkbox"/> AE United Arab Emirates | <input checked="" type="checkbox"/> LR Liberia |
| <input checked="" type="checkbox"/> AL Albania | <input checked="" type="checkbox"/> LS Lesotho |
| <input checked="" type="checkbox"/> AM Armenia | <input checked="" type="checkbox"/> LT Lithuania |
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| <input checked="" type="checkbox"/> AU Australia | <input checked="" type="checkbox"/> LV Latvia |
| <input checked="" type="checkbox"/> AZ Azerbaijan | <input checked="" type="checkbox"/> MA Morocco |
| <input checked="" type="checkbox"/> BA Bosnia and Herzegovina | <input checked="" type="checkbox"/> MD Republic of Moldova |
| <input checked="" type="checkbox"/> BB Barbados | <input checked="" type="checkbox"/> MG Madagascar |
| <input checked="" type="checkbox"/> BG Bulgaria | <input checked="" type="checkbox"/> MK The former Yugoslav Republic of Macedonia |
| <input checked="" type="checkbox"/> BR Brazil | |
| <input checked="" type="checkbox"/> BY Belarus | <input checked="" type="checkbox"/> MN Mongolia |
| <input checked="" type="checkbox"/> CA Canada | <input checked="" type="checkbox"/> MW Malawi |
| <input checked="" type="checkbox"/> CH and LI Switzerland and Liechtenstein | <input checked="" type="checkbox"/> MX Mexico |
| <input checked="" type="checkbox"/> CN China | <input checked="" type="checkbox"/> NO Norway |
| <input checked="" type="checkbox"/> CR Costa Rica | <input checked="" type="checkbox"/> NZ New Zealand |
| <input checked="" type="checkbox"/> CU Cuba | <input checked="" type="checkbox"/> PL Poland |
| <input checked="" type="checkbox"/> CZ Czech Republic | <input checked="" type="checkbox"/> PT Portugal |
| <input checked="" type="checkbox"/> DE Germany | <input checked="" type="checkbox"/> RO Romania |
| <input checked="" type="checkbox"/> DK Denmark | <input checked="" type="checkbox"/> RU Russian Federation |
| <input checked="" type="checkbox"/> DM Dominica | <input checked="" type="checkbox"/> SD Sudan |
| <input checked="" type="checkbox"/> EE Estonia | <input checked="" type="checkbox"/> SE Sweden |
| <input checked="" type="checkbox"/> ES Spain | <input checked="" type="checkbox"/> SG Singapore |
| <input checked="" type="checkbox"/> FI Finland | <input checked="" type="checkbox"/> SI Slovenia |
| <input checked="" type="checkbox"/> GB United Kingdom | <input checked="" type="checkbox"/> SK Slovakia |
| <input checked="" type="checkbox"/> GD Grenada | <input checked="" type="checkbox"/> SL Sierra Leone |
| <input checked="" type="checkbox"/> GE Georgia | <input checked="" type="checkbox"/> TJ Tajikistan |
| <input checked="" type="checkbox"/> GH Ghana | <input checked="" type="checkbox"/> TM Turkmenistan |
| <input checked="" type="checkbox"/> GM Gambia | <input checked="" type="checkbox"/> TR Turkey |
| <input checked="" type="checkbox"/> HR Croatia | <input checked="" type="checkbox"/> TT Trinidad and Tobago |
| <input checked="" type="checkbox"/> HU Hungary | <input checked="" type="checkbox"/> TZ United Republic of Tanzania |
| <input checked="" type="checkbox"/> ID Indonesia | <input checked="" type="checkbox"/> UA Ukraine |
| <input checked="" type="checkbox"/> IL Israel | <input checked="" type="checkbox"/> UG Uganda |
| <input checked="" type="checkbox"/> IN India | <input checked="" type="checkbox"/> US United States of America |
| <input checked="" type="checkbox"/> IS Iceland | |
| <input checked="" type="checkbox"/> JP Japan | <input checked="" type="checkbox"/> UZ Uzbekistan |
| <input checked="" type="checkbox"/> KE Kenya | <input checked="" type="checkbox"/> VN Viet Nam |
| <input checked="" type="checkbox"/> KG Kyrgyzstan | <input checked="" type="checkbox"/> YU Yugoslavia |
| <input checked="" type="checkbox"/> KP Democratic People's Republic of Korea | <input checked="" type="checkbox"/> ZA South Africa |
| | <input checked="" type="checkbox"/> ZW Zimbabwe |
| <input checked="" type="checkbox"/> KR Republic of Korea | Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet: |
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| <input checked="" type="checkbox"/> LC Saint Lucia | <input checked="" type="checkbox"/> |
| <input checked="" type="checkbox"/> LK Sri Lanka | |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit)

Box No. VI PRIORITY CLAIM		<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 01 JULY 1999	US09/345492	US		
item (2) 01 JULY 1999	US60/141827	US		
item (3)				
<input type="checkbox"/> The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s):				
* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.				
Box No. VII INTERNATIONAL SEARCHING AUTHORITY				
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority): Date (day/month/year) Number Country (or regional Office)		
ISA / EP				
Box No. VIII CHECK LIST; LANGUAGE OF FILING				
This international application contains the following number of sheets: request : 4 description (excluding sequence listing part) : 28 claims : 5 abstract : 1 drawings : 6 sequence listing part of description : 3 Total number of sheets : 47		This international application is accompanied by the item(s) marked below: 1. <input checked="" type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input checked="" type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):		
Figure of the drawings which should accompany the abstract: 3		Language of filing of the international application: ENGLISH		
Box No. IX SIGNATURE OF APPLICANT OR AGENT				
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).				
				
STRATAGEM INTELLECTUAL PROPERTY MANAGEMENT FOR AND BEHALF OF THE APPLICANTS				

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

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Date of receipt of the record copy by the International Bureau:

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's
file reference P1049/GW/THY

Applicant
GLAXO GROUP LIMITED

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE £55 T

2. SEARCH FEE £605 S

International search to be carried out by EP
(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 47 sheets.

first 30 sheets £264 b1

17 x £6 = £102 b2
remaining sheets additional amount

Add amounts entered at b1 and b2 and enter total at B £366 B

Designation Fees

The international application contains ALL designations.

8 x £56 = £448 D
number of designation fees payable (maximum 8) amount of designation fee

Add amounts entered at B and D and enter total at I £814 I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT (if applicable) P

5. TOTAL FEES PAYABLE £1474

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge
deposit account (see below)

☐ bank draft

☐ coupons

☒ cheque

☐ cash

☐ other (specify):

☐ postal money order

☐ revenue stamps

DEPOSIT ACCOUNT AUTHORIZATION (this mode of payment may not be available at all receiving Offices)

The RO/ is hereby authorized to charge the total fees indicated above to my deposit account.

☐ (this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account No.

Date (day/month/year)

Signature

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P1049/GW/THY	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB 00/ 02357	International filing date (day/month/year) 30/06/2000	(Earliest) Priority Date (day/month/year) 01/07/1999
Applicant GLAXO GROUP LIMITED		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☒ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

3

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02357

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/52 C12N15/53 C12N15/54 C12N15/55 C12N9/02
C12N9/10 C12N9/12 C12N9/78 C12N1/19 C12N1/21
C12R1/19 C12P19/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C12P C12R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, CAB Data, STRAND, EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
✓ A	WO 91 09130 A (CHEMGEN CORP) 27 June 1991 (1991-06-27) cited in the application the whole document ---	A
✓ A	EP 0 344 937 A (ICI PLC) 6 December 1989 (1989-12-06) the whole document ---	B
✓ A	EP 0 329 062 A (TAKEDA CHEMICAL INDUSTRIES LTD) 23 August 1989 (1989-08-23) the whole document ---	C
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

5 October 2000

Date of mailing of the international search report

20/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hornig, H

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02357

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
✓ A	F.C. HEIDHARDT ET AL.: "Escherichia coli and Salmonella" 1996, ASM PRESS, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US XP002149398 Chapter 35; J. NEUHARD and R.A. KLEIN; Biosynthesis and conversion of pyrimidines. page 580 -page 599 ---	D
✓ A	TSENG M-J ET AL: "TOTAL SEQUENCE FLANKING REGIONS AND TRANSCRIPTS OF BACTERIOPHAGE T4 NRDA GENE CODING FOR ALPHA CHAIN OF RIBONUCLEOSIDE DIPHOSPHATE REDUCTASE" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 263, no. 31, 1988, pages 16242-16251, XP002149394 ISSN: 0021-9258 cited in the application the whole document ---	E
✓ A	ALLEN J R ET AL: "T-4 RIBO NUCLEOTIDE REDUCTASE PHYSICAL AND KINETIC LINKAGE TO OTHER ENZYMES OF DEOXY RIBO NUCLEOTIDE BIOSYNTHESIS" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 255, no. 16, 1980, pages 7583-7588, XP002149395 ISSN: 0021-9258 cited in the application the whole document ---	F
✓ A	JI J ET AL: "T4 PHAGE RIBONUCLEOTIDE REDUCTASE ALLOSTERIC REGULATION IN-VIVO BY THYMIDINE TRIPHOSPHATE" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 266, no. 25, 1991, pages 16289-16292, XP002149396 ISSN: 0021-9258 the whole document ---	G
✓ A	HOLMGREN A: "GLUTATHIONE DEPENDENT ENZYME REACTIONS OF THE PHAGE T-4 RIBO NUCLEOTIDE REDUCTASE SYSTEM" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 253, no. 20, 1978, pages 7424-7430, XP002149397 EN ISSN: 0021-9258 the whole document ---	H
	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02357

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
✓ A	CARRERAS C W ET SANTI D V: "The catalytic mechanism and structure of thymidylate synthase" ANNUAL REVIEW OF BIOCHEMISTRY, US, PALTO ALTO, CA, vol. 64, 1995, pages 721-762, XP002093507 the whole document	I
✓ A	FOLLMANN H: "Enzymatic reduction of ribonucleotides: biosynthesis pathway of deoxyribonucleotides" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION, DE, VERLAG CHEMIE. WEINHEIM, vol. 13, no. 9, 1 September 1974 (1974-09-01), pages 569-579, XP002093150 ISSN: 0570-0833 the whole document	J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02357

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9109130 A	27-06-1991	US 5213972 A	25-05-1993
		AT 155170 T	15-07-1997
		AU 642199 B	14-10-1993
		AU 7037491 A	18-07-1991
		CA 2070826 A	09-06-1991
		DE 69031042 D	14-08-1997
		DE 69031042 T	26-02-1998
		DK 504279 T	02-03-1998
		EP 0504279 A	23-09-1992
		ES 2107451 T	01-12-1997
		GR 3024967 T	30-01-1998
		JP 3032292 B	10-04-2000
		JP 5504055 T	01-07-1993
		KR 180897 B	01-04-1999
EP 0344937 A	06-12-1989	AT 108487 T	15-07-1994
		AU 3580289 A	07-12-1989
		CA 1316476 A	20-04-1993
		DE 68916708 D	18-08-1994
		DE 68916708 T	01-12-1994
		JP 2039894 A	08-02-1990
		JP 2874761 B	24-03-1999
		US 5093244 A	03-03-1992
EP 0329062 A	23-08-1989	AT 105855 T	15-06-1994
		CN 1035129 A	30-08-1989
		DE 68915301 D	23-06-1994
		DE 68915301 T	22-09-1994
		ES 2052789 T	16-07-1994
		JP 2002349 A	08-01-1990

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

STRATAGEM INTELLECTUAL PROPERTY MAN-
AGEMENT
The old rectory
Nedging tye
Ipswich, IP7 7HQ
UNITED KINGDOM

Date of mailing
(day/month/year)

20/10/2000

Applicant's or agent's file reference

P1049/GW/THY

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/GB 00/ 02357

International filing date
(day/month/year)

30/06/2000

Applicant

GLAXO GROUP LIMITED

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Mireille Claudepierre

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

Copy for the Elected Office (EO/US)
PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

GLAXOSMITHKLINE
Two New Horizons Court
Brentford
Middlesex TW8 9EP
ROYAUME-UNI

RECEIVED

JUN 20 2002

TECH CENTER 1600/2900

Date of mailing (day/month/year) 05 February 2002 (05.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference P1049/GW/THY	
International application No. PCT/GB00/02357	International filing date (day/month/year) 30 June 2000 (30.06.00)

1. The following indications appeared on record concerning: <input checked="" type="checkbox"/> the applicant <input checked="" type="checkbox"/> the inventor <input type="checkbox"/> the agent <input type="checkbox"/> the common representative		
Name and Address WANG, Baomin 18716 Calypso Place Gaithersburg, MD 20879 United States of America	State of Nationality CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: <input type="checkbox"/> the person <input type="checkbox"/> the name <input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence		
Name and Address WANG, Baomin 13622 Pine View Lane Rockville, MD 20850 United States of America	State of Nationality CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to: <input checked="" type="checkbox"/> the receiving Office <input type="checkbox"/> the designated Offices concerned <input type="checkbox"/> the International Searching Authority <input checked="" type="checkbox"/> the elected Offices concerned <input type="checkbox"/> the International Preliminary Examining Authority <input type="checkbox"/> other:		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Elisabeth KÖNIG Telephone No.: (41-22) 338.83.38
---	---

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

GLAXOSMITHKLINE
Two New Horizons Court
Brentford
Middlesex TW8 9EP
ROYAUME-UNI

Date of mailing (day/month/year) 05 February 2002 (05.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference P1049/GW/THY	
International application No. PCT/GB00/02357	
	International filing date (day/month/year) 30 June 2000 (30.06.00)

1. The following indications appeared on record concerning:		
<input checked="" type="checkbox"/> the applicant	<input checked="" type="checkbox"/> the inventor	<input type="checkbox"/> the agent <input type="checkbox"/> the common representative
Name and Address LIU, Lin 18716 Calypso Place Gaithersburg, MD 20879 United States of America	State of Nationality CN	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
<input type="checkbox"/> the person	<input type="checkbox"/> the name	<input checked="" type="checkbox"/> the address <input type="checkbox"/> the nationality <input type="checkbox"/> the residence
Name and Address LIU, Lin 13622 Pine View Lane Rockville, MD 20850 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to:		
<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned	
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned	
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Elisabeth KÖNIG
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 11 July 2001 (11.07.01)	Applicant's or agent's file reference P1049/GW/THY
International application No. PCT/GB00/02357	Priority date (day/month/year) 01 July 1999 (01.07.99)
International filing date (day/month/year) 30 June 2000 (30.06.00)	
Applicant ANDERSON, David, Martin et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 31 January 2001 (31.01.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).



The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer I. Britel Telephone No.: (41-22) 338.83.38
--	--

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PX3813/WO		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB00/02357	International filing date (day/month/year) 30/06/2000	Priority date (day/month/year) 01/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/52		
Applicant GLAXO GROUP LIMITED et al.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application 		
Date of submission of the demand 31/01/2001		Date of completion of this report 16.10.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Roscoe, R Telephone No. +49 89 2399 2554 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/GB00/02357

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-28 as originally filed

Claims, No.:

1-48 as originally filed

Drawings, sheets:

1/7-7/7 as originally filed

Sequence listing part of the description, pages:

1-3, filed with the letter of 21.08.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02357

- ☐ the description, pages:
- ☒ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1, 3, 5, 6, 11-14, 21, 22, 26-28, 32-39, 45-48 (all part).

because:

- ☒ the said international application, or the said claims Nos. 1, 3, 5, 6, 11-14, 21, 22, 26-28, 32-39, 45-48 (all part) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02357

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
- ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
- ☒ the parts relating to claims Nos. 2, 4, 7-10, 15-20, 23-25, 29-31, 40-44 and 1, 3, 5, 6, 11-14, 21, 22, 26-28, 32-39, 45-48 (all part).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-48
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 1-48
Industrial applicability (IA)	Yes: Claims 1-48
	No: Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

III. No Opinion

Expressed for invention group III (see section IV)

IV. Lack of Unity

Applicant has paid one additional search fee. Hence, invention groups I and II, as defined below are the subject of examination.

- I. Claims relating to constructs and their uses having genes encoding (A) ribonucleotide reductase and (B) thioredoxin: 2, 7-10, 15-20, 23-25, 29, 30, 40-44 and 1, 5, 6, 11-14, 21, 22, 26-28, 33-39, 45-48 (all part)
- II. Claims relating to constructs and their uses having genes encoding (C) uridine kinase alone or in combination with (D) dCTP deaminase: 4, 31 and 1, 3, 5, 6, 11-14, 21, 22, 26-28, 32-39, 45-48 (all part)
- III. Claims relating to constructs and their uses having genes encoding (D): 1, 3, 5, 6, 11-14, 21, 22, 26-28, 32-39, 45-48 (all part)

The above invention groups are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

Each of these claim groups relates to a technically different aspect of a method of pyrimidine deoxyribonucleoside production. D1 already provides various methods of pyrimidine deoxyribonucleoside production and hence there is no novel unifying concept spanning the above invention groups. Each of the different invention groups relates to the use of a specific gene or pair of genes which have no common technical or functional features and solve the problem of providing further methods of pyrimidine deoxyribonucleoside production in different way.

V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability

D1 relates to pyrimidine deoxyribonucleoside production. Fig.1 shows the biochemical pathway involved. Reference on p.4 suggests that dcd is the key enzyme. Suggests introducing a PdNPase (Pyrimidine deoxyribonucleoside phosphohydrolase) into strains e.g. thymidilate phosphohydrolase. Viewing claims 1 and 10, this enzyme can itself be a thioredoxin reductase / thymidylate synthase. Can additionally introduce mutations or additional metabolic gene-encoding DNA (p.16, I.5-8). Suggests introducing thymidylate synthase (td) mutation which prevents dUMP > TMP and thus results in accumulation of the former. Suggests using endproduct resistance mutations (p.24) and that additional metabolic gene-encoding DNA can be ndk or dcd (p.29) or thioredoxin.

D2 uses Brevibacterium to produce thymidine - irrelevant. D3 discloses DNA encoding pyrimidine analog resistance gene region derived from Bacillus, which allows transformants to produce large amounts of uracil / uridine - irrelevant. D4 is a general review on biosynthesis of pyrimidines. States on p.593 that E. coli dcd mutants have reduced dTTP pools. D5 discloses sequencing of T4 nrdA gene. On p.16249, col.1, it is stated that the T4 enzyme does not suffer from inhibition as much as the E. coli enzyme. D6 is a paper working with crude extracts of T4-infected E. coli cells which shows that a multienzyme aggregate associated with ribonucleotide reductase delivers DNA precursors to the replication apparatus. D7 shows that T4 nrdA can be inhibited by dTTP, but that this effect is lost with increasing purity of the preparation. D8 is a 1978 paper disclosing that have found T4 infection of E. coli to involve induction of T4-encoded ribonucleotide reductase and thioredoxin. D9 is a review article on thymidylate synthase, D10 a review article on nrds (p.575 has table showing effect of nucleoside triphosphates on reduction of ribonucleotides).

- Novelty (Art.33(2) PCT)

The present claims appear to relate to novel selections from the metabolic genes suggested for use in pyrimidine biosynthesis in D1.

- **Inventive Step (Art.33(3) PCT)**

The expression of e.g. 2 genes from a single transcriptional unit as opposed to two individual units is a routine option for the skilled person which he would readily consider in the present context. Thus inventive step needs to be sought in the specific combinations of genes used. Page 29 of D1 clearly suggests that could use DNAs encoding amongst other enzymes; ribonucleoside diphosphate reductase (nrd), dCTP deaminase (dcd), thioredoxin (trxA) and a nucleoside diphosphate kinases (which includes ndk). Hence, all options are effectively selections from D1, although each is not explicitly disclosed.

Regarding the particular combinations of genes, each of these need to be considered separately.

Coexpression of ribonucleotide reductase and thioredoxin (Invention Group I) is obvious since the enzymes functionally interact (cooperate). Further, even if limit this aspect of invention to T4 enzymes, the reduced level of allosteric interaction was known (e.g. D5 or D7) and hence obviously advantageous to use T4 enzymes in present context (problem stated by applicant at top of p.7 of the description cannot be taken into account because constructs of claims have no features addressing putative lethality problem).

The second invention group relates to the expression of uridine kinase with or without dCTP deaminase. The expression of uridine kinase was stated to be inventive since, according to applicant, it was not known to have a direct role in pyrimidine biosynthesis. However, the author of D1 clearly thought that udk would enhance pyrimidine biosynthesis, otherwise he would not have suggested using it in the context of pyrimidine biosynthesis. Further addition of the dCTP deaminase to the construct is considered as an additional selection of a pyrimidine biosynthesis gene combination lacking any surprising effect.

Hence, the present claims lack inventive step.

- **Industrial Applicability (Art.33(4) PCT)**

The present claims appear to have industrial applicability.

VIII. Certain observations

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB00/02357

Claim 1 is worded in an ambiguous manner. If the named enzymes are listed A-D, corresponding to their order in the claim, then claim can be understood as for example:

- (i) (A and B) or (C and/or D)
- (ii) A and (B or C) and/or D
- (iii) A and (B or (C and/or D))

Each of these options provides with different combinations. The description seems to favour interpretation (i) slightly, yet in view of the prior art D1 which applicant must be aware of this would make little sense, since D1 already envisages constructs having only C or only D. Basically the wording of the claim needs to be unambiguous and the interpretation chosen clearly based on an identified passage of the application as originally filed. Further, once the wording is clarified, it will be necessary to ensure that the rest of the claims are consistent therewith. *It is noted that it may be more practical to delay this clarification until the regional phase since the invention groups will need to be separated therein.*

PATENT COOPERATION TREATY

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NOTIFICATION OF TRANSMITTAL OF
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EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference PX3813/WO		IMPORTANT NOTIFICATION
International application No. PCT/GB00/02357	International filing date (day/month/year) 30/06/2000	Priority date (day/month/year) 01/07/1999
Applicant GLAXO GROUP LIMITED et al.		


1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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